REMARKS

Claims 1-29 are pending in the application.

Claims 1, 4, 8-9, 11-12, 15 and 19-29 are amended above to primarily to convert allowable claims into independent format or to further distinguish the claimed invention from the prior art.

No new matter has been added to the application by way of these specification and claim amendments.

I. THE ALLOWABLE SUBJECT MATTER

Applicants note that claims 4, 5, 8-11, 15-16, 19, 20, 24-25 and 28-29 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form, and thanks the Examiner in this regard. Applicants have amended these claims above to convert them into an allowable form

II. THE SECTION 101 CLAIM REJECTION

The examiner rejected claim 21 for being directed to non-statutory subject matter.

Claim 21 is amended above in a manner that causes the claim to encompass statutory subject matter.

III. THE OBVIOUSNESS REJECTION

Claims 1-3, 6-7, 12-14, 17-18, 21-23 and 26-27, are rejected under 35 U.S.C. 103(a) as being unpatentable over Cabib et al (U.S. patent 5,991,028) in view of Lee al (U.S. patent 5,978,497). The rejected claims are patentable at least because the cited prior art does not disclose several elements of the amended independent claims and because of the examiner's improper combination of prior art references.

A. The Cited Prior Art Does Not Disclose Automated Techniques For Determining Nuclear Pleomorphism By Calculating Image Region Shape Factors From The Perimeters And Areas Of Identified Image Regions And Assessing Pleomorphism From The Shape Factors' Statistical Parameters As Claimed

Regarding claim 1, the Examiner states that Cabib discloses a method of histological assessment of nuclear pleomorphism by identifying image regions potentially corresponding to cell nuclei in histological image data (column 27, lines 29-37, histological types of intraductal carcinoma have been recognized: comedo *(a collection of cells)*, cribriform *(perforate, sieve-like)*, micropapillary *(small conical projections)* and solid: *(NB definitions taken from Chambers Dictionary of Science and Technology, Harrap Publishers 1999)*. The Examiner quotes Cabib column 6 line 66 to column 7 line 3, i.e. "All *(i.e. these intraductal carcinomas)* are recognized and classified by specific criteria and subdivided primarily by architectural pattern, cellular pleomorphism *(multiple shapes of cell - not multiple shapes of cell nucleus)* and nuclear hyperchromasia *(excessively pigmented cell nuclei)*.

To distinguish more clearly over Cabib, Applicants have now amended independent claims 1, 12 and 21 to limit them as follows:

a) the image regions comprise respective groups of contiguous pixels *(see Applicants' specification at page 6 line 27 to page 7 line 5)*, and

b) the image is rendered binary with identified image regions and background distinguished from one another by association with different binary digits *(see Applicants' specification at page 7 lines 3-4 and 18-19 re a group of contiguous pixels of pixel value 1, and page 7 lines 27-28 re pixels with a background value (0));*

Cabib discloses a spectroscopic or spectral technique for bio-imaging. The Cabib technique can be used for automatic and/or semiautomatic spectrally resolved morphometric classification (e.g. grading) of cells (e.g., neoplasm) – see e.g. column 8 lines 23-26. The technique involves classifying pixels individually in an image of a sample containing at least part of a cell; each pixel is classified into one of several classification groups according to its spectrum - see e.g. column 25 lines 21-23; and the classification groups are analysed to classify a cell into a cell class - see column 8 lines 33-43.

Cabib mentions pleomorphism twice. The first mention is in the context of cellular pleomorphism *(i.e. multiple shapes of cell, not cell nucleus)* at column 6 line 67 to column 7 line 1 in referring to the contents of a prior art scientific paper of Page et al. Nuclear pleomorphism *(i.e. multiple shapes of cell nucleus)* is mentioned once in Cabib at column 27 lines 39-44 in referring to the contents of another prior art scientific paper of Gallagher et al. However, unlike Applicants' invention as now claimed in independent claims 1, 12 and 21, Cabib makes no disclosure whatsoever regarding any automated technique for determining nuclear pleomorphism by calculating image region shape factors from the perimeters and areas of identified image regions and assessing pleomorphism from the shape factors' statistical parameters. For at least this reason, claims 1-3, 6-7, 12-14, 17-18, 21-23 and 26-27 are non-obvious and patentable. The reason Cabib makes no disclosure whatsoever regarding assessing pleomorphism from statistical parameters of image region shape factors is simple. Cabib uses a quite different technique for which image regions, image region shape factors, and statistical parameters of image region shape factors are absolutely irrelevant. In particular, Cabib examines each pixel in an image individually to determine its spectrum, all pixels are inevitably the same shape, and pixel shape factor information is therefore quite useless; unlike Applicants' invention, Cabib does not examine image regions which are groups of contiguous (touching) pixels.

As has been said, the Cabib technique involves classifying individual pixels into classification groups and analysing the groups to classify a cell. (See Cabib at column 8 lines 33-43). Column 34 lines 1-9 discloses eight classes into which Cabib classifies cancer cells: e.g. situ-duct-solid (FIG. 14a, class 1); infiltrating-duct-solid 5 (FIG. 14e, class 2); in situ duct cribriform (FIG. 14b, class 3); infiltrating duct cribriform (FIG. 14f, class 4); in situ duct comedo (FIG. 14c, class 5); infiltrating duct comedo (FIG. 14g, class 6); in situ lobular carcinoma (FIG. 14d, class 7); and infiltrating lobular carcinoma. Applicants' invention as now claimed in claims 1, 12 and 21 is concerned only with nuclear pleomorphism, not with any other aspect of cancer cells.

In this connection, Cabib discloses a spectral library constructed of six separate spectral groups for use in classifying pixels. (See Cabib column 28 lines 36-37). Moreover, Cabib column 27 lines 1-14 discloses classifying pixels using a neural network algorithm which associates a pixel with a classification group according to the pixel's spectrum. Pixels placed in a

classification group via this algorithm are presented in an image by a preselected artificial colour. Alternatively, such pixels may be presented as an abundance histogram, which can be used for cell classification by means of a second neural network algorithm which associates abundance histograms with cell classes. This is of course completely different to Applicants' invention as now claimed in Independent claims 1, 12 and 21, which uses image region shape factors not artificial colour or abundance histograms to assess nuclear pleomorphism from the shape factors' statistical parameters.

In the last paragraph of page 3 of the Official Action, the Examiner appears to indicate that Cabib column 29, lines 37-50 and FIGS. 7a-h and 8a-h discloses determining perimeters and areas of identified image regions, calculating image region shape factors from the perimeters and areas and assessing pleomorphism from the shape factors' statistical parameters. This is respectfully traversed, because that is not what the cited section of Cabib discloses. Cabib column 29, lines 37-50 actually discloses area covered by each of the six classified spectral regions appearing in each cell nucleus. Such an area is not the area of a cell nucleus - instead it is the area of part of a cell nucleus having particular spectral characteristics. Moreover, unlike Applicants' invention as now claimed in independent claims 1, 12 and 21, in Cabib column 29, lines 37-50 there is no disclosure whatsoever regarding image regions' perimeters or shape factors, or assessing pleomorphism from shape factors' statistical parameters.

Also in the last paragraph of page 3 of the Official Action, the Examiner goes on to quote most of the sentence in Cabib column 29, lines 37-49 beginning "As was determined by the classification map algorithm", but does not say why. Applicants do not understand the relevance of this quote to the claimed invention, because (as already discussed) it merely discloses a cell classification technique based on pixel spectra, which is quite different to Applicants' invention as now claimed in independent claims 1, 12 and 21.

The Examiner points out that Cabib column 33, lines 29-36 discloses the classifying network option of defining a 'non classified' pixel with a definition depends on the user through a threshold decision. However, this appears to be merely equivalent to Lee column 27, lines 17-25 and FIG. 6B, indicating that classification can be unreliable for objects with features close to decision boundaries: i.e. a small variation in feature values could change the classification result.

Cabib's 'non classified' pixel appears to be indicating something similar, i.e. some pixels should be left without classification because the classification result is too uncertain.

B. The Combination of Cabib With Lee Does Render The Claims Obvious

The Examiner acknowledges that Cabib does not explicitly state "the method including thresholding the image data to render it binary". Moreover, the Applicants have amended independent claims 1, 12 and 21 such that they are now limited to image regions comprising respective groups of contiguous pixels and the image being rendered binary with identified image regions and background distinguished from one another by association with different binary digits, which Cabib also does not disclose.

The Examiner cites Lee in combination with Cabib to provide disclosure of thresholding. Lee discloses a threshold test and a threshold image to detect objects of interest at column 8, lines 27-29. In column 9, lines 21-32 of Lee, a first offset is subtracted from the threshold image and a second offset is added to the threshold image to create low and high threshold images respectively and the threshold image itself is designated a medium threshold image. The Examiner states that "it would have been obvious to one having ordinary skill ..... to modify Cabib ... according ... Lee because it provides technique to identify objects of interest and creates a threshold image, which *(sic)* applied to the enhanced images that can easily be implemented in an imaging device.". This rejection is traversed, because, in brief (and discussed later in more detail):

a) it is submitted that Lee and Cabib are not properly combined;

b) Cabib has no use for Lee's threshold image or objects of interest (i.e. groups of pixels) - Cabib examines pixels individually not in groups and their shapes are all identical; and

c) in any event the combination of Cabib and Lee fails to render Applicants' invention obvious as now claimed in claims 1, 12 and 21 because neither Cabib nor Lee discloses obtaining shape factors from image region perimeters and areas and assessing pleomorphism from the shape factors' statistical parameters: instead Cabib classifies cells from individual pixel spectra, and Lee is concerned with distinguishing abnormal cell types from artefacts and normal cell types – see column 54 lines 63-67 and cell types and artefacts in column 55.

Claims 1-3, 6-7, 12-14, 17-18, 21-23 and 26-27 are also not obvious at least because Cabib cannot use a threshold image which identifies objects of interest (groups of pixels) in an image. This is because Cabib examines pixels individually not in groups. Instead the Cabib

technique involves classifying each individual pixel (not a group of pixels) in an image - a pixel is classified into a classification group according to its spectrum (variation of intensity with wavelength or colour) irrespective of whether or not it is above or below a threshold - see e.g. column 25 lines 21-23.

Cabib mentions the use of a threshold in column 19 lines 42-59 in connection with assigning a pixel (x,y) to a class on the basis of the deviation e_i^2 of that pixel's spectrum from a known spectrum of a fluorophore attached to cell type i. In this regard, if e_i^2 is more than a threshold for all cells of type i = 1 to k, but less than that threshold for i = k + 1, then the image point or pixel (x,y) can be classified as class k + 1. This Cabib teaching clearly has nothing whatsoever to do with Lee's image thresholding to identify objects of interest, because a single pixel is not a group of pixels and therefore also not an object of interest, and moreover the pixel is already identified in the image and requires no thresholding to identify it.

Cabib also refers to the use of a threshold in column 26 line 39 and column 30 lines 30-33. However, both of these references relate to the use of a threshold to determine whether or not to classify a spectrum as "not classified". This also clearly has nothing whatsoever to do with Lee's image thresholding to identify objects of interest, because a pixel spectrum is not a group of pixels and therefore it also is not an object of interest.

Consequently Lee and Cabib are not properly combined, because Cabib has no possible need or even use for Lee's image thresholding to identify objects of interest: in the absence of such need, one of ordinary skill in the art reading Cabib would have no motivation to search for a reference such as Lee to image thresholding to identify objects of interest.

Moreover, even if Lee and Cabib were to be read together, no useful result would emerge because there is nothing in Cabib to apply image thresholding to usefully. Moreover, neither reference discloses assessing nuclear pleomorphism from image region shape factors' statistical parameters. If the Examiner maintains this objection, Applicants would be grateful for the column and line number(s) in Cabib where motivation to search for Lee appears, and for a more detailed account of how Cabib would make use of the results of Lee's image thresholding to identify objects of interest.

C. Many Dependent Claims Are Independently Non-Obvious And Patentable

Turning now to claim 2, the Examiner states that Cabib discloses a method according to claim 1 wherein the shape factors' statistical parameters comprise at least one of their mean, weighted mean, median, mode, maximum and minimum, and refers to Cabib at column 17, lines 33-43 for supplying this teaching. The examiner's position is respectfully traversed, because here again it is completely contrary to the facts. Cabib column 17, lines 33-43 actually makes no disclosure whatsoever regarding any of the following: (a) image regions, (b) image region shape factors, (c) shape factors' statistical parameters, (d) shape factors' mean, (e) shape factors' median, (f) shape factors' mode, (g) shape factors' maximum or (h) shape factors' minimum.

The Examiner also quotes column 17, lines 33-41, i.e. in brief that Equation 6 provides a general weighting response function $w(\lambda)$ for computing gray scale images, and enabling display of an RGB colour image. However, Applicants do not understand the reason for this quote because a weighting response function $w(\lambda)$ for computing gray scale images has nothing whatsoever to do with shape factors or their mean, weighted mean, median, mode, maximum or minimum. Instead, column 17, lines 40-43 indicates that a weighting response function $w(\lambda)$ enables display of a conventional RGB colour image and non-conventional (pseudo) colour images. Cabib's weighting response function $w(\lambda)$ is completely irrelevant to assessing pleomorphism from shape factors' statistical parameters comprising at least one of their mean, weighted mean, median, mode, maximum and minimum as per claim 2 and claim 2 is non-obvious and patentable at least for this reason.

Turning now to claim 3, neither Cabib nor Lee discloses Otsu thresholding.

CONCLUSION

All claims 1-29 are believed to be ready for patenting for the reasons recited above. Favorable reconsideration and allowance of all pending application claims is, therefore courteously solicited.

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